Fibrinolysis

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Fibrinolysis is the process wherein a fibrin clot, the product of coagulation, is broken down.[1] Its main enzyme plasmin cuts the fibrin mesh at various places, leading to the production of circulating fragments that are cleared by other proteases or by the kidney and liver.

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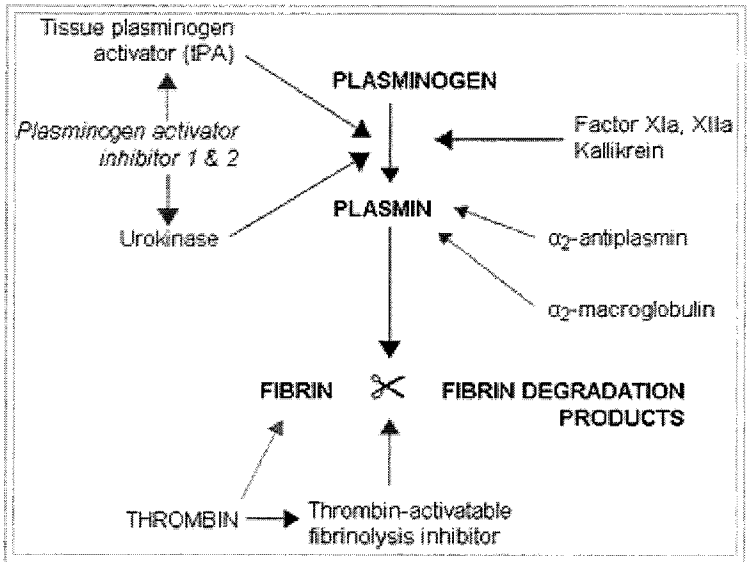
Physiology

Plasmin is produced in an inactive form, plasminogen, in the liver. Although plasminogen cannot cleave fibrin, it still has an affinity for it, and is incorporated into the clot when it is formed.



Fibrinolysis (simplified). Blue arrows denote stimulation, and red arrows inhibition.

Plasminogen contains secondary structure motifs known as kringles, which bind specifically to lysine and arginine residues on fibrin(ogen). When converted from plasminogen into plasmin, it functions as a serine protease, cutting C-terminal to these lysine and arginine residues. Fibrin monomers, when polymerized, form protofibrils. These protofibrils contain two strands, anti-parallel, associated non-covalently. Within a single strand, the fibrin monomers are covalently linked through the actions of coagulation factor XIII. Thus, plasmin action on a clot initially creates nicks in the fibrin; further digestion leads to solubilization.[2]

Tissue plasminogen activator (t-PA)[3] and urokinase are the agents that convert plasminogen to the active plasmin, thus allowing fibrinolysis to occur. t-PA is released into the blood very slowly by the damaged endothelium of the blood vessels, such that, after several days (when the bleeding has stopped), the clot is broken down. This occurs because plasminogen became entrapped within the clot when it formed; as it is slowly activated, it breaks down the fibrin mesh. t-PA and urokinase are themselves inhibited by plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2 (PAI-1 and PAI-2). In contrast, plasmin further stimulates plasmin generation by producing more active forms

of both tPA and urokinase.

Alpha 2-antiplasmin and alpha 2-macroglobulin inactivate plasmin. Plasmin activity is also reduced by thrombin-activatable fibrinolysis inhibitor (TAFI), which modifies fibrin to make it more resistant to the tPA-mediated plasminogen.

Measurement

When plasmin breaks down fibrin, a number of soluble parts are produced. These are called fibrin degradation products (FDPs). FDPs compete with thrombin, and so slow down the conversion of fibrinogen to fibrin (and thus slows down clot formation). Similar results are also seen after administration of DDAVP or after severe stress.[4] A more rapid detection of fibrinolytic activity, especially hyperfibrinolysis, is possible with thromboelastometry (TEM) in whole blood, even in patients on heparin. With various assays an enhanced fibrinolysis becomes visible in the curve signature and from the calculated values, e.g. the maximum lysis parameter. A special test for the identification of increased fibrinolysis (APTEM) compares the TEM profile in the absence or presence of the fibrinolysis inhibitor aprotinin. In severe cases of activated fibrinolysis, this assay confirms the syndrome already in less than 15 min during the early phases of clot formation [5]

Role in disease

Few congenital disorders of the fibrinolytic system have been documented. Nevertheless, excess levels of PAI and alpha 2-antiplasmin have been implicated in the metabolic syndrome and various other disease states.

However, acquired disturbance of fibrinolysis (Hyperfibrinolysis), is not uncommon. Many trauma patients suffer from an overwhelming activation of tissue factor and thus massive hyperfibrinolysis.[6] Also in other disease states hyperfibrinolysis may occur. It could lead to massive bleeding if not diagnosed and treated early enough.

The fibrinolytic system is closely linked to control of inflammation, and plays a role in disease states associated with inflammation. Plasmin, in addition to lysing fibrin clots, also cleaves the complement system component C3, and fibrin degradation products have some vascular permeability inducing effects.

Pharmacology

Fibrinolytic drugs are given after a heart attack to dissolve the thrombus blocking the coronary artery, experimentally in stroke to reperfuse the affected part of the brain, and in massive pulmonary embolism. The process is called thrombolysis.

Antifibrinolytics, such as aminocaproic acid (ε-aminocaproic acid) and tranexamic acid are used as inhibitors of fibrinolysis. Their application may be beneficial in patients with hyperfibrinolysis because they arrest bleeding rapidly if the other components of the haemostatic system are not severely affected. This may help to avoid the use of blood products such as fresh frozen plasma with its associated risks of infections or anaphylactic reactions. The antifibrinolytic drug aprotinin was abandoned after identification of major side effects, especially on kidney.

References

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External links

- Graphical representation of the fibrinolytic pathway

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